Sphingolipids: a novel target in the treatment of Alzheimer Disease?

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Country

Netherlands

Title of project or programme

Sphingolipids: a novel target in the treatment of Alzheimer Disease?

Source of funding information

ZonMw

Total sum awarded (Euro)

€ 1,500,000

Start date of award

01/12/2014

Total duration of award in years

4.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract
Key features of Alzheimer’s disease (AD) pathology are aggregates of amyloid-ß peptides, neurofibrillary tangles, blood-brain barrier (BBB) damage and neuroinflammation. Elucidation of the deregulated biological mechanisms that lead to the onset and progression of AD is critical to identify new treatment strategies.
We hypothesize that early in the disease process, an altered balance between the different

classes of sphingolipids (SL), including ceramides and sphingomyelins, plays a key role in disease onset and progression. Using a translational approach, we therefore aim to identify the role of SL metabolism in AD and models thereof and reveal if pharmacological modulation of this pathway using already approved drugs is beneficial in slowing down the disease process.
To address this hypothesis we will:
1. Quantify SL and involved enzymes in different forms and subtypes of dementia and correlate the SL levels and enzymatic activity to associated neuropathology, as determined by the level of neuroinflammation, changes at the BBB and neurodegeneration in selected brain regions.
2. Correlate the SL profiles identified in body fluids (plasma and CSF) to clinical features, including cognitive decline in humans and in AD mouse models at different disease stages and during normal brain aging, to identify specific SL patterns that can be used as biomarkers of early disease progression.
3. Explore whether modulation of the SL pathway via existing compounds (FTY-720P, a S1P analogue) reduces inflammatory events and promotes neuronal survival using human in vitro models.
4. Provide the first proof-of-concept that pharmacological modulation of SL metabolism using existing drugs in animal models of AD prevents and/or retards disease progression.
The proposed preclinical studies are essential to:
(i) Identify which asymptomatic elderly individuals might benefit from SL modulation for the prevention or delay of AD.
(ii) Provide the first proof-of-concept data to establish that an approved drug approved for other indications is effective for AD.
(iii) Develop targeted therapies for select patient subgroups by stratifying patients according to their levels of SL metabolites.
(iv) Design targeted clinical trials which can dramatically reduce the number of patients required for the study and the associated costs.
(v) Proceed directly to phase I/II clinical trials in AD with a Food and Drug Administration (FDA) approved drug, with a novel application in AD.
Ultimately, this research will be the first proof-of-concept study to test the feasibility and relevance of the personalized medicine approach in the area of SL.

Lay Summary
Further information available at:

Types:
Investments > €500k

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Netherlands

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Alzheimer's disease & other dementias

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2016

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N/A

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